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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,757	02/11/2004	Michel Pairet	01-1174-1-C1	3466

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MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368

EXAMINER	
BADIO, BARBARA P	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,757	PAIRET ET AL.	
	Examiner	Art Unit	
	Barbara P. Badio, Ph.D.	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,15-23,25-39 and 63-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,15-23,25-39 and 63-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/086,145.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Nonfinal Office Action on the Merits

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

2. Claims 1, 3-10, 15-23, 25-39 and 63-66 are pending in the present application and will be examined according to MPEP § 803.02.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim1, 3-10, 15-23, 25-39 and 63-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enantiomers and racemates, does not reasonably provide enablement for solvates and hydrates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in making an enablement rejection are summarized as:

a) the quantity of experimentation necessary,

b) the amount of direction or guidance presented,

c) the presence or absence of working examples,

d) the nature of the invention,

e) the state of the prior art,

f) the relative skill of those in the art,

g) the predictability or unpredictability of the art, and

h) the breadth of the claims.

In re Colianni, 195 USPQ 150 (CCPA 1977). *In re Rainer*, et al., 146 USPQ 218 (CCPA 1965). *Ex parte Formal*, 230 USPQ 546 (BPAI 1986).

a) Determining if a particular compound would form a solvate or hydrate would require synthesis and recrystallization of the compound solvate or hydrate using a variety of solvents, temperatures and humidities. The experimentation for solvates or hydrates is potentially open-ended.

b) The specification merely mentions the Applicant's intention to make solvates and hydrates, without teaching the preparation thereof.

c) While the claims recite solvates and hydrates, no working examples show their formation. As stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, 1194 (Fed.Cir. 1993):

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The specification shows no evidence of the formation and actual existence of solvates and hydrates. Hence, Applicant must show formation of solvates and hydrates or limit the claims accordingly.

d) The nature of the invention is chemical synthesis of solvates and hydrates, which involves chemical reactions.

e) The state of the art recognizes that the formation, composition and therapeutic activity of solvates and hydrates are unpredictable. The Federal Circuit has recognized a solvate as an example of a polymorph or pseudopolymorph (emphasis added):

> "Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon) .... [P]seudopolymorphs are often loosely called polymorphs ... Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a solvate, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.

SmithKline Beecham Corp. v. Apotex Corp., 74 USPQ2d 1398, 1409 (Fed.Cir. 2005).

The same rationale obtains for hydrates; solvates in which the solvent is water. Souillac, et al., Characterization of Delivery Systems, Differential Scanning Calorimetry, pages 217-218 (in Encyclopedia of Controlled Drug Delivery, 1999, John Wiley & Sons, pages 212-227), recognize that different polymorphs of the same drug can have different therapeutic activity (emphasis added):

> Because different polymorphic forms of the same drug exhibit significant differences in their physical characteristics, therapeutic activity from one form to another may be different. Studying the polymorphism of a drug

and the relative stability of the different polymorphs is a critical part of pre-formulation development.

Further, Vippagunta et al. (Advanced Drug Delivery Reviews, 48 (2001), pages 3-26) state "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated in to the crystal lattice of a compound is complex and difficult." See page 18, section 3.4.

f) The artisan using Applicant's disclosure to prepare the claimed solvates and hydrates would be, e.g., an experienced process chemist with at least a BS chemistry degree.

g) Chemical reactions are known as unpredictable. *In re Marzocchi, et al.*, 169 USPQ 367, 370 (CCPA 1971); *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). See above regarding the unpredictability of solvate and hydrate formation.

h) The breadth of the claims includes thousands of steroids and tiotropium salts as well as presently unknown compounds embraced by the terms solvates and hydrates. See MPEP 2164.01(a), discussed supra, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicant's claimed invention.

Double Patenting

5. The rejection of claim 1 on the ground of nonstatutory obviousness-type double patenting over claim 1 of Drechsel et al. (US 6,890,517) is withdrawn.

The terminal disclaimer filed April 4, 2008 is noted.

6. The provisional rejections of claim 1 on the ground of nonstatutory obviousness-type double patenting over claims of copending Applications 11/006,940; 11/068,134; 11/109,094; 11/169,876; 11/267,354 and 11/424,244 are maintained and claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims of copending Applications 10/392,558 and 10/735,959.

Applicant's argument that the provisional rejections be withdrawn in accordance with MPEP § 804(I)(B)(1) is noted. However, this is not the only rejection of record.

As with copending Applications 11/006,940; 11/068,134; 11/109,094; 11/169,876; 11/267,354 and 11/424,244, each of copending Applications 10/392,558 and 10/735,959 is inclusive of a composition comprising/consisting essentially of tiotropium. The compositions of the instant claims differ in the recitation of a "steroid". However, because the art teaches combination of anticholinergic agent with steroids (corticosteroids) for use in treating respiratory conditions such as asthma, the addition of steroids to the compositions of 10/392,558 and 10/735,959 would be prima facie obvious. Therefore, the instant claims are rendered obvious.

For these reasons and those given in the previous Office Action, the provisional rejections of claim 1 on the ground of nonstatutory obviousness-type double patenting over claims of copending Applications 11/006,940; 11/068,134; 11/109,094; 11/169,876; 11/267,354 and 11/424,244 are maintained and claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims of copending Applications 10/392,558 and 10/735,959.

Claim Rejections - 35 USC § 103

7. The rejection of claim 24 under 35 USC 103(a) over Magee et al. (US 2002/0111495) is made moot by the cancellation of the instant claim.

8. The rejection of claims 1, 3-10. 15-23, 25-39 and 63-66 under 35 USC 103(a) over Magee et al. (US 2002/0111495) is withdrawn.

9. Claims 1, 3-10, 15-23, 25-39 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishimura et al. (Allergology International, 1999) and Banholzer et al. (US 5,610,163) in combination.

Nishimura et al. teaches an inhalation composition comprising anticholinergic agents, such as, oxitropium bromide and ipratropium bromide and corticosteroids such as beclomethasone dipropionate for treating asthma (see the entire article, especially page 85, col. 2, Introduction; page 87, Table 1 and Discussion). Nishimura teaches the addition of oxitropium bromide to beclomethasone dipropionate shows beneficial effects (see page 87, col. 1, Discussion, 1st paragraph).

Banholzer et al. teaches thienyl carboxylic acids such as tiotropium and its salts as strong anticholinergic agents for use in treating asthma (see the entire article, especially col. 3, line 23 – col. 4, line 9; col. 5, compound A). Banholzer also teaches the compounds show similar toxicity to ipratropium bromide while at the same time the therapeutic effect is stronger (see col. 3, lines 27-32).

The combination of the above cited references makes obvious the utilization of a composition comprising an anticholinergic agent, including tiotropium bromide and a corticosteroid, including beclomethasone dipropionate in the treatment of asthma. The motivation to combine an anticholinergic agent with a corticosteroid is based on the teaching by Nishimura of the beneficial effect of said combination. The motivation to utilize tiotropium salts in said composition is based on the teaching of Banholzer of the increase therapeutic effect over ipratropium bromide.

The recitation of (a) corticosteroids such as budesonide and fluticasone (see claim 6); (b) weight ratios of anticholinergic to steroid (see claims 9 and 10); (c) particle size of excipients (see claims 15-22); (d) capsule containing the claimed composition (see claims 25-38) and (e) a kit containing the claimed composition (see claims 63-66) are noted.

However, (a) Nishimura broadly teaches the use of corticosteroids and the recited corticosteroids are well known in the art and (b) Banholzer teaches various formulations including capsules (see '163, col. 4, lines 3-9). Additionally, the recitation of particle size; weight ratio of the active ingredients and kits are not patentable over the prior art as discussed above because (a) the court has held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233 and (b) incorporation of known agents into kits are well known in the medical art. Therefore, the instantly claimed invention would have been obvious to one of skilled in the art at the time of the present invention.

Telephone Inquiry

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Barbara P. Badio, Ph.D. whose telephone number is 571-272-0609. The examiner can normally be reached on M-F from 6:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Barbara P. Badio, Ph.D./
Primary Examiner, Art Unit 1612